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Methylsulfinyl Carbanion

I. Preparation of Ethers

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Tertiary and secondary alcohols were titrated with a standardised solution of sodium methylsulfinyl carbanion, and the alkoxide ions formed were alkylated. By this method ethers were readily prepared from different alcohols, including some containing other characteristic groups, *viz.* esters, ketones, tertiary amines, and olefins.

Sodium methylsulfinyl carbanion (sodium methylsulfinylmethanide) is formed on the addition of sodium hydride to an excess of dimethyl sulfoxide.[1,2] Dissolved in dimethyl sulfoxide, its conjugate anion is a very powerful base.[1] It readily abstracts protons from compounds with active hydrogens, *e.g.* alcohols. Such compounds can conveniently be titrated[3] with a standardised solution of methylsulfinyl carbanion. Triphenylmethane is a suitable indicator as the deep red colour of the triphenylmethyl anion immediately appears in the presence of excess methylsulfinyl carbanion.

Ethers are usually prepared from alcohols by alkylation with alkyl sulfates or alkyl halides. The alkylating agent reacts with the anion of the alcohol obtained by treating the alcohol with base, *e.g.* aqueous sodium hydroxide,[4] sodium hydroxide in dimethylformamide or dimethyl sulfoxide,[5,6] or sodium in liquid ammonia.[7] These combinations of bases and solvents, however, are not always suitable for converting alcohols into the corresponding alkoxide ions. Limited solubility of the alcohol or insufficient strength of the base may slow down or inhibit the reaction. Side reactions with other groups in the molecule may also cause complications.

It independently occurred to us that ethers should be formed readily by treating an alcohol with an equivalent amount of sodium methylsulfinyl carbanion followed by an alkylating agent. The advantages should be several; methylsulfinyl carbanion is a very strong base, anions are only weakly solvated [8] while cations are well solvated in dimethyl sulfoxide,[9] alcohols are

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easily titrated with a standardised solution of methylsulfinyl carbanion,[3] and finally dimethyl sulfoxide is a very good solvent for most alcohols.[9]

Using this method we have successfully prepared ethers of various secondary and tertiary alcohols. We have alkylated rapidly and at room temperature, *tert*-butyl alcohol, *tert*-amyl alcohol, triphenylmethanol, the saturated tertiary sesquiterpene alcohol cedrol, and the unsaturated monoterpene alcohol α-terpineol.

Methylsulfinyl carbanion is reported to react with aldehydes, ketones, and esters, giving β-hydroxy sulfoxides and β-keto sulfoxides.[10,11] This side reaction might interfere in alkylations of alcohols containing aldehyde, ketone, or ester functions. However, we found that methyl benzilate, *N*-ethyl-3-piperidyl benzilate, methyl β-hydroxy-β-phenylpropionate, and methyl α-cyclohexyl-α-phenylglycolate were alkylated without the carbonyl function being affected. Methyl α-cyclohexyl-α-phenylglycolate has been reported to withstand repeated treatment with methyl iodide and silver oxide.[12] It was readily methylated by the procedure described above in a yield of 65 %. 5,5-Dimethylcyclohexane-1,3-dione (dimedone) was cleanly *O*-alkylated without trace of *C*-alkylation. Attempts to alkylate 1-(2,6-dimethylphenyl)-3-(4-morfolinyl)-2-propanol by known methods gave a quaternised product. Using the methylsulfinyl carbanion method the desired *O*-alkylated product could be isolated in an excellent yield.

Efforts to alkylate an α-hydroxy ketone or a β-hydroxy ketone were not successful. From 3-hydroxy-2-butanone only a tarry residue was obtained. On alkylation of 4-hydroxy-4-methyl-2-pentanone, acetone was isolated as the main product. This indicates that the dominant reaction is a retrograde aldol condensation. Neither could a β-hydroxy aldehyde, such as aldol, be alkylated.

We have found no example where an alcohol containing a carbonyl group could be titrated by methylsulfinyl carbanion to a definite end point. The bright red colour of the triphenylmethyl anion was not distinctly seen. The reaction between methylsulfinyl carbanion and the carbonyl group mentioned above[10,11] is a possible reason for this.

Triphenylmethyl anion reacts with molecular oxygen giving the anion of triphenylcarbinol.[13] The disappearance of the red colour, sometimes met with after a titration, may be attributed to this reaction.

In 1964 Hakomori reported[14] the permethylation of glycolipid and polysaccharide by the methylsulfinyl carbanion method. On the alkylation of oestriol, we independently found[15] that the method is useful for alkylation of compounds with more than one alcohol group in the molecule.

EXPERIMENTAL

General procedure. Sodium methylsulfinyl carbanion (sodium methylsulfinylmethanide) was prepared according to Corey and Chaykovsky [1] with the modifications by Sjöberg [2] and standardised with formanilide.

The alcohol was dissolved or dispersed in a small amount of dry dimethyl sulfoxide in a dry flask and a trace of triphenylmethane added. An equivalent amount of sodium methylsulfinyl carbanion was introduced from a pipette with stirring and external cooling. The bright red solution formed was directly treated with a 10 % excess of an alkylating agent, *e.g.* dimethyl sulfate, diethyl sulfate, or methyl iodide. Cooling and stirring were

continued for 10 min. If the cooling is too effective, dimethyl sulfoxide, m.p. 18°, will crystallize. The ether obtained often separated as a clear almost colourless upper layer and could be collected directly. If two layers did not form, methylene chloride and water were added. The layers were separated and the aqueous dimethyl sulfoxide layer was extracted with methylene chloride. The combined extracts were washed free from dimethyl sulfoxide with water and dried over magnesium sulfate. The solvent was removed and the obtained ether distilled or recrystallized. For the characterisation of the ethers prepared, see Table 1.

Table 1.

Alcohol	Alkylating agent	Alkyl ether				
		B.p.	B.p. ref.	Analyses	Yield %	Ref.
tert-Butyl alcohol	Dimethyl sulfate	55–56°	55–56°	[a,b]	78	16
tert-Butyl alcohol	Methyl iodide	54–56°	55–56°	[a,b]	52	16
tert-Butyl alcohol	Diethyl sulfate	71–73°	73°	[a,b]	61	17
tert-Amyl alcohol	Dimethyl sulfate	85–87°	86°	[a,b]	81	18
tert-Amyl alcohol	Diethyl sulfate	98–99°	101°	[a,b]	62	18
Cedrol	Dimethyl sulfate	110–112°/1 mm	–	[a,c,d]	73	
α-Terpineol	Dimethyl sulfate	80–82°/11 mm	212°	[a,c]	82	19
Triphenylmethanol	Dimethyl sulfate	79–81° (m.p.)	83–84° (m.p.)	[a]	92	20
1-(2,6-Dimethylphenyl)-3-(4-morpholinyl)-2-propanol	Dimethyl sulfate	141–143°/0.4 mm		[a,c,e]	90	21[g]
Methyl benzilate	Dimethyl sulfate	163–165°/10 mm	191°/16 mm	[a]	86	22
N-Ethyl-3-piperidyl benzilate	Diethyl sulfate	170–173°/0.4 mm	–	[a,b,c]	88	12
Methyl α-cyclohexyl-α-phenylglycolate	Dimethyl sulfate		41–43° (m.p.)	[a,b,c]	65	12
Methyl β-hydroxy-β-phenylpropionate	Dimethyl sulfate	83–85°/0.6 mm	–	[a,f]	60	
Dimedone	Dimethyl sulfate	124–126°/12 mm	132–135°/15 mm	[a,c]	65	23

[a] IR spectrum. [b] Comparison with authentic sample (IR and/or NMR). [c] NMR spectrum. [d] Calc. for $C_{16}H_{28}O$: C 81.3; H 11.9. Found: C 81.1; H 11.9. [e] Equiv. weight calc. for $C_{16}H_{25}NO_2$: 263. Found: 267. The base was titrated with 0.1 N perchloric acid in glacial acetic acid. [f] Calc. for $C_{11}H_{14}O_3$: C 68.0; H 7.27; O 24.7. Found: C 68.4; H 7.32; O 24.5. [g] Refers to preparation of 1-diethylamino-3-(2,6-dimethylphenyl)-2-propanol.

IR and/or NMR spectra indicate the presence of methoxyl or ethoxyl groups and absence of hydroxyl groups in the compounds isolated.

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